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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,947	07/25/2001	Bjorn Dahlback	INL-036DV	7730

22832 7590 04/10/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
04/10/2008	PAPER

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BJORN DAHLBACK

Appeal 2007-4130
Application 09/912,947
Technology Center 1600

Decided: April 10, 2008

Before RICHARD E. SCHAFER, SALLY GARDNER LANE, and MICHAEL P. TIERNEY *Administrative Patent Judges*.

LANE, *Administrative Patent Judge*.

DECISION ON APPEAL

I. STATEMENT OF THE CASE

Appellant appeals under 35 U.S.C. § 134 from the final rejection of claims 46, 53-55, 64, and 65. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the rejection.

The application was filed on July 25, 2001. The real parties in interest are said to be T.A.C. Thrombosis and Coagulation AB and Instrumentation Laboratory S.p.A. (App. Br. at 2).

The claimed invention is directed to a method for detecting individuals at risk for developing thrombosis and for determining the

presence of a Factor V gene mutation associated with Activated Protein C (APC)-resistance in an individual at risk for APC-resistance. (*Id.* at 4).

The Examiner rejected claims 46, 53-55, 64, and 65 under 35 U.S.C. § 112, first paragraph, for lack of an enabling specification.

In support of this rejection the Examiner relied upon the following references[1]:

- Pennisi, "A Closer Look at SNPs Suggests Difficulties," *Science*, vol. 281, pp. 1787-89 (1998) ("Pennisi").
- Blumenfeld, et al., WO 99/52942, published Oct. 21, 1999 ("Blumenfeld").
- de Visser, et al., "The HR2 Haplotype of Factor V: Effects on Factor V Levels Normalized Activated Protein C Sensitivity Ratios and the Risk of Venous Thrombosis," *Thromb. Haemost.*, vol. 83, pp. 577-82 (2000) ("de Visser").
- Bertina, "Genetic Approach to Thrombophilia," *Thromb Haemost.*, vol. 86, pp. 92-103 (2001) ("Bertina").
- Price, "Factor V Leiden Mutation and the Risks for Thromboembolic Disease: A Clinical Perspective," *Ann. Intern. Med.*, vol. 127, pp. 895-903 (1997) ("Price").

[1] The Examiner's Answer includes a new ground of rejection because additional references were cited. *See* Bd. R. 39(a)(2). The statutory basis for ground of rejection in the Final Office Action remained the same. (*See* Ans. at 2-3).

II. FINDINGS OF FACT

The record supports the following findings of fact, as well as any other findings of fact set forth in this decision by a preponderance of the evidence.

1. Independent claim 46 recites:

> A method for detecting an individual at risk of developing thrombosis, said method comprising:
> (a) obtaining a sample from the individual;
> (b) conducting a nucleic acid assay on the sample, wherein the nucleic acid assay is a hybridization assay or a sequencing assay;
> (c) determining abnormal presence or absence of at least one nucleic acid fragment or sequence in the individual's Factor V gene compared to a normal control; and
> (d) detecting the individual at risk of developing thrombosis based on the determination of step (c).

2. Claim 46 does not recite any specific type of thrombosis.
3. Claim 46 is directed to a method based on nucleic acid hybridization or sequencing.
4. Claim 46 requires determining, in an individual, the "abnormal presence or absence of at least one nucleic acid fragment or sequence in the individual's Factor V gene compared to a normal control", i.e., determining if there is a mutation in the Factor V gene, that is related to an increased risk of developing thrombosis.
5. Claim 46 is not limited to any specific mutation of the Factor V gene.
6. Appellant's Specification does not provide a clear definition of the phrase "an individual at risk of developing thrombosis" which appears in claim 46.

7. The ordinary meaning of the phrase "an individual at risk of developing thrombosis" is an individual who "is more likely to develop thrombosis than a normal individual" as agreed to by Appellant. (*See* App. Br. at 8).

8. Independent claim 54 recites:

> A method for determining a presence of a Factor V gene mutation associated with Activated Protein C (APC)-resistance in an individual at risk for APC-resistance, the method comprising the steps of
>
> (a) obtaining a sample from the individual;
>
> (b) conducting a nucleic acid sequencing assay on the sample using reagents specific for the Factor V gene to determine the Factor V gene sequence; and
>
> (c) determining the presence of the Factor V gene mutation associated with APC resistance in the individual by comparing the sequence of the Factor V gene from step (b) to a normal Factor V gene sequence.

9. Claim 54 does not recite any specific mutation of the Factor V gene.

10. Appellant's Specification does not provide a clear definition of the phrase "an individual at risk for APC-resistance" which appears in claim 54.

11. The ordinary meaning of the phrase "an individual at risk for APC-resistance" is an individual who "is more likely to develop APC-resistance than a normal individual", which comports with Appellant's argument on how we should construe a person "at risk" of a condition. (*Cf.* App. Br. at 8).

12. Appellant's Specification does not provide any means of determining which individuals are "more likely to develop APC-resistance than a normal individual."

13. The Specification states:

> Recent results have shown in a conventional DNA-linkage study of a large family with inherited APC resistance that there is a strong linkage between a neutral polymorphism in the Factor V gene and expression of APC-resistance. This strongly suggests that a mutation in the Factor V gene is the cause for APC-resistance. This is conclusive evidence that nucleic acid hybridisation assays, as well as nucleic acid sequencing can be used in conventional ways in order to detect individuals at risk for thrombotic events due to a low level of APC-cofactor 2 activity. Thus, these types of assays may be used for checking, in an individual, the abnormal presence or absence of one or more nucleic acid fragment(s) and/or sequence(s) unique for the presence or absence of expression of a Factor V molecule either carrying APC-cofactor 2 activity or being deficient in this activity. The protocols and conditions are the same as normally applied for other genes, except for now using reagents specific for the Factor V gene and, optionally, mutation(s) associated with APC-resistance or specific for a normal Factor V gene. Any cell sample from the individual may be appropriate.

(Substitute Spec. at ¶ [0081]).

14. The Specification refers to a linkage between inherited APC resistance and the "neutral polymorphism." (*Id.*).

15. Appellant acknowledges that the Specification does not provide the exact structure of the "neutral polymorphism," nor does it teach any other specific abnormalities or mutations in the Factor V gene that would be associated with a risk of developing thrombosis or a risk of APC-resistance. (App. Br. at 5).

16. The Specification provides no working examples of detecting an individual at risk of developing thrombosis or determining a presence of a Factor V gene mutation associated with a risk for APC-resistance.
17. Pennisi reported on the progress of the study of a gene, the *LPL* gene, which has a specific mutation known to cause high blood lipid concentrations and an increased incidence of heart disease in some families. (Pennisi at 1787).
18. As reported in Pennisi, attempts to "find out which, if any, *LPL* gene variants [also called single-nucleotide polymorphisms or SNPs] might be increasing the risk for heart disease in the general population," became very difficult when it was discovered that the gene had undergone considerable recombination, which made it "difficult if not impossible" to even "construct a tree representing the historical sequence of mutations that gave rise to the SNPs." (Pennisi at 1787).
19. Pennisi also reported that a similar study to find all of the SNPs in the β-globin gene, which has "long been known to cause sickle cell anemia" (*id.*), provided "nowhere near enough information to find something unusual and say 'there's a disease gene.'" (*Id.* at 1788).
20. In Pennisi, one researcher is quoted as saying: "There has been this naïve idea that once you've gotten to the gene, you'll be able to decide which is the [pertinent] mutation. . . . But this is going to be very hard." (*Id.*)

21. Another researcher quoted in Pennisi, remarked: "You can't have just SNPs on their own[.] You must have [other information and technology] to go with it." (*Id.*).

22. In regard to the size of the studies needed to interpret data on gene mutations for correlation with disease, Pennisi reported:

> Others at the meeting pointed out that association studies require that researchers look at much larger numbers of people than typical family studies, to sift out the false signals. "It's not enough to have 70 controls and 50 patients," says Gert-Jan Van Ommen, head of the Human Genome Organization and a geneticist at Sylvius Laboratories in Lieden, Netherlands. "You're talking about requiring populations of several thousand."

(*Id.* at 1789).

23. Blumenfeld reports studies of gene mutations and polymorphisms in relation to disease risk and diagnosis, specifically, the *FLAP* gene and its relationship to leukotriene diseases, such as asthma. (Blumenfeld at abstract).

24. Figure 3 of Blumenfeld compares the association of several polymorphisms of the *FLAP* gene, here called "biallelic markers," with incidence of asthma. (*Id.* at 6).

25. In Figure 3, the marker 10-35/390 is shown to be associated with asthma in a statistically significant association (p value of 0.00229), while the marker 10-33/327 is associated with asthma with no statistical association (p value of 0.294). (*Id.* at Figure 3).

26. Blumenfeld reports that "the biallelic marker 10-35/390 presented a strong association with asthma, this association being highly significant (pvalue = 2.29×10^{-3}). The two markers 10-32/357 and

10-33/234 showed weak association when tested independently." (*Id.* at 106).

27. Bertina reports "the progress in our search for genetic risk factors for venous thrombosis." (Bertina at introduction).

28. Bertina notes:

> At the end of the year 2000, we can find at least two genetic risk factors in 13% of the thrombophilia families, one genetic risk factor in 60% of the families and no genetic risk factor at all in 27% of the families. Considering the strong support for familial thrombophilia being an oligogenetic disease [citations omitted], we must conclude that we still lack information on several genetic factors contributing to the risk of venous thrombosis.

(*Id* at 92).

29. After reviewing genetic studies of thrombotic risk, Bertina reports:

> All studies have investigated the effect of a particular SNP on the risk of venous thrombosis. There are, however, considerable differences in the selection of patients; first events/recurrent events, consecutive patients/selected patients, deep-vein thrombosis/all thrombotic events. Of course this may influence the outcome of the studies as well as the extent of agreement that can be obtained between studies of the same genotype in different centers. Also, a polymorphism might differ in its effect on different phenotypic expressions of venous thrombosis. For example, factor V Leiden [a specific polymorphism] is a risk factor for deep-vein thrombosis, cerebral vein thrombosis, superficial vein thrombosis and portal vein thrombosis, but not for primary pulmonary embolism and retinal vein thrombosis. Finally, differences in exposure to environmental factors may influence the results. The use of oral contraceptive enhances the risk of factor V Leiden and prothrombin 20210 A alleles, while there is no interaction between these alleles and surgery. Thus, Factor V Leiden is not an important risk factor for postoperative thrombosis in patients undergoing hip arthroplasty, while the D allele of the

> polymorphism in intron 16 of the gene coding for the angiotensin-I converting enzyme increases the risk almost tenfold.

(*Id.* at 96-97) (citations omitted).

30. de Visser reports the results of a study of a specific haplotype, which comprises two polymorphisms of the factor V gene in association with the risk of venous thrombosis or reduced sensitivity to APC. (de Visser at abstract).
31. de Visser reports: "Our results show that the HR2 haplotype is not associated with an increased risk of venous thrombosis or with a reduced sensitivity for APC in non-FVL [factor V Leiden] carriers. However, the HR2 haplotype is associated with a reduced sensitivity for APC in carriers of FVL and with reduced factor V antigen levels." (de Visser at abstract).
32. Price "review[s] clinical data on factor V Leiden mutation, with emphasis on prevalence of and risks for thromboembolism and implications for screening and management." (Price at "Purpose").
33. Price reports: "Factor V Leiden mutation is associated with three- to sixfold increase in risks for primary and recurrent venous thromboembolism, especially in patients without transient risk factors, such as surgery or trauma. . . . Factor V Leiden mutation does not seem to increase risks for arterial thrombosis." (*Id.* at "Data Synthesis").
34. Shen et al., "The Serine Protease Cofactor Factor V Is Synthesized by Lymphocytes," *J. Immunol.*, vol. 150, pp. 2992-301 (1993)

("Shen"), discloses the cDNA sequence of Factor V mRNA cloned from human lymphoid cells. (Shen at Fig. 3).

35. The analysis of the Factor V cDNA sequence in Shen revealed:

> Both strands from 14 independent recombinant plasmid clones carrying the amplified F7/F8 factor V cDNA fragment were sequenced. Six nucleotide base substitutions were identified (Fig. 3). Two substitutions, from thymine to cytosine and from cytosine to thymine at positions 2209 and 2236, respectively, were silent mutations. The remaining four guanine to adenine base substitutions resulted in a silent mutation at position 2302 and amino acid changes from arginine to lysine at position 2573, from arginine to histidine at position 2595, and from glutamic acid to lysine at position 2773. These deduced amino acid changes are conservative substitutions and may not significantly affect factor V function or only subtly. In addition, half of the clones (seven of 14) have an adenine to guanine substitution at position 2290, a silent substitution, which abolished the *EcoRI* site.

(Shen at 2996).

36. Shen does not disclose the results of any functional assays to determine whether the conservative substitutions "may not significantly affect factor V function or only subtly." (*Id.*).

37. Voorberg, et al., "Association of idiopathic venous with single point mutation at Arg^{506} of factor V," *Lancet*, vol. 343, pp. 1535-36 (1994) ("Voorberg"), discloses experiments that relate to mutations in the Factor V gene and defective APC activity.

38. Voorberg states that the results it discloses "suggest that a molecular abnormality in factor V underlies the thrombotic events that are associated with a defective anticoagulant response to APC in vitro. We report linkages between resistance to APC and a

single point-mutation at a putative APC cleavage site at Arg^{506} of factor V." (Voorberg at 1535).

39. To determine this linkage, Voorberg screened 27 patients with "(recurrent) idiopathic episodes of thromboembolism." (*Id.*).

40. Voorberg reported that

> 10 of the 27 patients were heterozygous for the Arg^{506} to Gln^{506} mutation. 8 of the 27 (30%) had an abnormal APC sensitivity ratio ($\leq$ 2.0), in agreement with the frequency in similar cohorts. [citations omitted] The abnormal APC sensitivity ratio was significantly linked to the Arg^{506} to Gln mutation (figure 2; *U* test, $p<0.0001$). In 3 patients who were heterozygous for the Arg^{506}Gln mutation, APC ratio was just above 2.0, and in only 1 patient did an abnormal APC sensitivity ratio (1.9) coincide with the normal Arg^{506}/Arg^{506} genotype.

(*Id.*).

III. ISSUES

The issue is whether the Examiner erred in rejecting claims 46, 53-55, 64, and 65 as lacking an enabling disclosure required under 35 U.S.C. § 112, first paragraph.

IV. LEGAL PRINCIPLES

The first paragraph of 35 U.S.C. § 112 requires that a claimed invention be "enabled" by the specification, wherein "the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same. . . " are disclosed. "To satisfy the enablement requirement of § 112, ¶ 1, a patent application must adequately disclose the claimed invention so as to enable a person skilled in the art to practice the invention at the time the application was filed without undue experimentation." *In re Swartz*, 232 F.3d 862, 863 (Fed. Cir. 2000).

"A specification need not disclose what is well known in the art." See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1385 (Fed. Cir. 1986). However, "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

The scope of the claims must not be broader than the scope of the enabling description in the specification. *See Nat'l Recovery Tech., Inc. v. Magnetic Separation Systems, Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999). "The scope of enablement, in turn, is that which is disclosed in the

specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." (*Id.*).

"[S]ome experimentation such as routine screening" is not undue. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). To determine whether the necessary experimentation is undue, we look at factors including "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Id.* at 737.

In the mechanical arts, unpredictability is not often an issue, because "a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws." *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970). In contrast, arts based on chemical reactions and physiological activity may be unpredictable. *Id.* "In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *Id.*

V. ANALYSIS

The Examiner rejected claims 46, 53-55, 64, and 65 as lacking the enabling disclosure required under 35 U.S.C. § 112, first paragraph. Because Appellant has argued the patentability of these claims as two separate groups, those dependent on claim 46 and those dependent on claim 54, we will discuss these two groups separately.

Claims 46, 53, 64, and 65

We select claim 46 is representative of claims 46, 53, 64, and 65. Bd. R. 37(c)(1)(vii).

Claim 46 recites:

> A method for detecting an individual at risk of developing thrombosis, said method comprising:
> (a) obtaining a sample from the individual;
> (b) conducting a nucleic acid assay on the sample, wherein the nucleic acid assay is a hybridization assay or a sequencing assay;
> (c) determining abnormal presence or absence of at least one nucleic acid fragment or sequence in the individual's Factor V gene compared to a normal control; and
> (d) detecting the individual at risk of developing thrombosis based on the determination of step (c).

As noted by the Examiner "the nature of the invention requires the knowledge of a mutation or abnormal presence or absence of a nucleic acid fragment or sequence in the Factor V gene which is associated with a risk of developing thrombosis and/or APC resistance." (Ans. at 4). Appellant acknowledges that the Specification provides no structures of any specific abnormalities or mutations of the Factor V gene that are determinative of a risk of developing thrombosis. (FF 15). In addition, there are no working examples that show using an abnormality in the Factor V gene to detect an individual at risk of developing thrombosis. (FF 16).

Claim 46 is not limited to any specific nucleic acid abnormality (FF 5) or any specific type of thrombosis (FF 2). We give claim 46 its broadest reasonable interpretation in view of the specification. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow."). Claim 46 encompasses the genus of all thromboses and the genus of all abnormalities.

The references cited by the Examiner demonstrate that it was unpredictable whether a particular mutation in the Factor V gene would be associated with any type of thrombosis. For example, the Examiner cited Pennisi and Blumenfeld as reports of what was known in the general field of polymorphisms, i.e. mutations, and disease risk. Pennisi quotes several geneticists as casting doubt that mere knowledge of polymorphisms would lead to direct correlations with disease or risk of disease. (FF 17-22). Blumenfeld discusses a specific example of a gene, other than the Factor V gene, which has several known polymorphisms, but teaches that some of these polymorphisms are correlated with disease and others are not. (FF 23-26).

The Examiner also cited references that specifically report on the knowledge of thrombosis or APC-resistance. For example, Bertina reported that there were two genetic risk factors for thrombophilia in 13% of the families tested, and one genetic risk factor in 60%. (FF 28). Twenty-seven percent of the families studied, though, had no genetic risk factors. (*Id.*). From these results, the authors of Bertina concluded, "we still lack information on several genetic factors contributing to the risk of venous thrombosis." (*Id.*).

Bertina continues by producing a complicated picture of some of the correlations between one polymorphism of the Factor V gene, Factor V Leiden, and the risk of different types of thrombosis. Factor V Leiden was reported to be a risk factor for deep-vein thrombosis, cerebral vein thrombosis, superficial vein thrombosis, and portal vein thrombosis, but not for primary pulmonary embolism, retinal vein thrombosis, or postoperative thrombosis in patients undergoing hip arthroplasty. (FF 29).

The Examiner also cited de Visser as reporting that a haplotype of the Factor V gene, called HR2, showed no association with increased risk of thrombosis or reduced APC-sensitivity in certain genetic backgrounds, but did show an association with these conditions in other backgrounds. (FF 30-31).

Finally, the Examiner cited Price to show that the Factor V Leiden mutation was thought to be associated with an increased risk of venous thrombosis, but not arterial thrombosis. (FF 32-33).

We agree with the Examiner that these references show that linking thrombosis or APC-resistance to genetic polymorphisms was unpredictable at the time of filing. (Ans. at 11). According to the Examiner, without disclosure of specific structures of abnormalities, "[t]he skilled artisan would have to perform an extremely large study and include different populations to determine if in fact there was either an association between each mutation, abnormal nucleotide acid fragment and sequence of factor V gene in individuals with any type of thrombosis." (Ans. at 11). We agree with the Examiner.

The unpredictability of the field of detecting risk of disease from genetic polymorphisms, the amount of work needed to determine associations between nucleic acid abnormalities and risk of disease, the breadth of Appellant's claims, and the lack of disclosure of specific abnormal nucleic acid structures in the Specification, indicate that carrying out the claimed method would require undue experimentation. Appellant's Specification does not disclose even a single mutation that would lead to an increased risk of thrombosis. While the Specification alleges a relationship between a Factor V mutation, for which no structure is provided, and APC

resistance (FF 13), there is no direction as to how one skilled in the art would have determined which mutations of the Factor V gene would lead to the APC resistance and increased risk of thrombosis. "It is not enough that a person skilled in the art, by carrying on investigations along the line indicated in the instant application, and by a great amount of work eventually might find out how to make and use the instant invention. The statute [35 U.S.C. §112, ¶1] requires the application itself to inform, not to direct others to find out for themselves," *Application of Scarbrough*, 500 F.2d 560, 565 (CCPA 1974).

Appellant argued that the scope of the claims is more limited than the Examiner considered:

> Claim 46 does not require detecting an individual who will develop thrombosis with 100% certainty. Claim 46 also does not require detecting an individual at risk of developing a particular type of thrombosis. Nor does claim 46 require detecting an individual at risk of developing all types of thrombosis. In another word [sic], claim 46 does not require association of one particular abnormal sequence in the Factor V gene with one particular type of thrombosis, such as, deep-vein thrombosis, cerebral vein thrombosis, superficial vein thrombosis, portal vein thrombosis, primary pulmonary embolism, or retinal vein thrombosis. Claim 46 also does not require association of one particular abnormal sequence in the Factor V gene with all types of thrombosis as described above. Such associations come into existence later in the art and are improvement inventions based on the disclosure of the present invention. Claim 46, on the other hand, is directed to the seminal discovery of the direct link between the Factor V gene and APC-resistance and increased risk for thrombosis.

(Reply Br. at 8). Appellant has not directed us to a portion of its Specification that limits claim 46 to any specific type of thrombosis or to

any specific Factor V mutation. Giving claim 46 its broadest reasonable interpretation in view of the Specification, *Zletz, supra*, we conclude that the scope of Appellant's claims includes subject matter of the genus of all thrombosis and all Factor V mutations that lead to increased risk of thrombosis. The Specification must enable the subject matter as broadly as it is claimed. *See Nat'l Recovery, supra.*

Appellant disagreed that knowledge of a mutation or abnormality in the Factor V gene is necessary to carry out the claimed method. Instead, Appellant argued that the Specification "provides extensive clinical and biochemical evidence leading to the conclusion that Factor V has a novel anticoagulant activity and that deficiency of such activity causes thrombosis associated with APC-resistance." (App. Br. at 7). Appellant concluded that "[t]he present disclosure and claimed invention, however, does not rely on the nature of this polymorphism to establish the association between Factor V and thrombosis/APC-resistance." (*Id.* at 8).

This argument is not persuasive, though, because claim 46 is directed towards "conducting a nucleic acid assay on a sample . . . ." (FF 1). Appellant has not directed us to evidence sufficient to show that his Specification supported or that it was known in the art that any Factor V mutation would lead to an increased risk of thrombosis.

Appellant attempted to show that it would have been predictable to determine which nucleic acid abnormalities would determine a risk for thrombosis by arguing:

> Detection of a mutation manifested by at least one abnormal nucleic acid fragment or sequence in an individual's Factor V gene would be sufficient to indicate that the individual is more likely to develop thrombosis than a normal individual because

> the Factor V gene containing an abnormal nucleic acid fragment or sequence is more likely to have an abnormal anticoagulant activity compared to a normal Factor V gene. Similar correlation between defects in genes without knowledge of the specific mutation and disease is known in the medical arts. For example, it has been well accepted that an individual is more likely to develop cancer than a normal individual if the individual's p53 gene (tumor suppressor gene) contains a mutation *(i.e.,* abnormal nucleic acid fragment or sequence) compared to a normal control, even if the specific nature of the mutation is unknown.

(App. Br. at 8). No declarations, affidavits, or even citation to references were provided to support the argument that one skilled in the art need not have been informed of any particular Factor V mutation associated with an increased risk of thrombosis in order to practice the claimed invention. Nor has Appellant presented evidence supporting its argument regarding the p53 gene, which we assume to be unrelated to the Factor V gene at any rate. Presented with only attorney argument, we do not accept that those in the art would have known that any "abnormal nucleic acid fragment or sequence" would inevitably lead to abnormal anticoagulant activity. Attorney argument is not evidence. *See In re Knowlton,* 500 F.2d 566, 572, n.4 (C.C.P.A. 1974) ("But for [one] reference, the record consists solely of the arguments and opinions of appellant's attorney—there are no affidavits in the record before us which set forth any *facts* whatsoever. Factual affidavits could have certainly been of help as, at least, some evidence on the question of enablement.").

Appellant also argued that the claimed method is enabled because there was a "high level of skill in the art of Factor V gene and protein in 1993" (*id.* at 9), and that "all of the methods needed to detect abnormal

presence or absence of a nucleic acid fragment or sequence in the Factor V gene were well known in the art when the application was filed." (*Id.* at 10). Furthermore, Appellant cites Shen as "discuss[ing] in detail that there are certain mutations in the Factor V gene that are silent or only cause conservative substitutions and may not significantly or only subtly affect the Factor V protein function. See, page 2996, left column of Evidence Appendix G." (*Id.* at 11).

Appellant has not convinced us that one skilled in the art could have determined which specific Factor V mutations are associated with an increased risk of developing thrombosis without the need for undue experimentation. Shen, which provides the Factor V cDNA sequence indicates that it is not predictable whether a difference in nucleotides results in an amino acid change that is significant, stating: "These deduced amino acid changes are conservative substitutions and may not significantly affect factor V function *or only subtly*." (FF 35 (emphasis added)). Shen does not continue with functional studies showing whether, in fact, the "conservative" changes have any effect (FF 36). Shen is persuasive evidence that those in the art would not have known which Factor V nucleotide abnormalities, i.e., mutations, would be predictive of an increased risk for thrombosis.

Appellant argued that the Examiner failed to cite prior art disclosing a linkage between the Factor V gene and APC-resistance or risk for thrombosis stating that the Examiner inappropriately relied on Bertina, de Visser, and Price, to show unpredictability in the art because

> the Examiner may not use the post-filing date reference to demonstrate that the invention is not enabled unless a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date or if a

> later-dated reference provides evidence that the disclosed invention was not possible at the time of filing.

(Reply Br. at 4-5). Appellant's argument misses the mark. The relevant inquiry before us is whether the specification enabled the claims as of the filing date of the present application, i.e., July 25, 1991. *See Reiffen v. Microsoft Corp.,* 214 F.3d 1342, 1345 (Fed. Cir. 2000) ("For purposes of § 112 ¶ 1, the relevant specifications are those of the [instant] patent; earlier specifications are relevant only when the benefit of an earlier filing date is sought under 35 U.S.C. § 120."). The references by Bertina, de Visser, and Price were published before, not after, Appellant's filing date of July 25, 2001, and thus are not "post-filing date" references.

Appellant asserted that the claimed method is a "pioneer invention," *see In re Hogan*, 559 F.2d 595, 606 (Fed. Cir. 1977), based on the discovery "for the first time ever that Factor V has a novel anticoagulant activity and the deficiency of such activity causes Activated Protein C (APC) resistance and associated thrombosis" (Reply Br. at 5). We note that even if the claimed methods are a "pioneer invention," the standard of enablement is not lowered. *See Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.,* 315 F.3d 1335, 1339-1342 (Fed. Cir. 2003).

Appellant argued that Bertina, de Visser, and Price provide evidence for enablement because each "demonstrates that an abnormal sequence (i. e., a mutation or a polymorphism) in the Factor V gene was found to be associated with at least one type of thrombosis in at least some populations." (Reply Br. at 9). As we discussed above, these references do not teach that there is a simple or straightforward relationship between abnormalities in the Factor V gene and an increased risk of thrombosis. Instead, the references

present a complex picture of some correlations that were found with some abnormalities and some types of thrombosis, but not others. (*See* FF 27-33). Indeed, the authors of Bertina concluded "we still lack information on several genetic factors contributing to the risk of venous thrombosis." (FF 23).

Appellant has not provided evidence showing that the mutations discussed in the references to Bertina, de Visser, and Price would have been sufficient to enable the full scope of Appellant's claim 46. Instead these references indicated that it would have been difficult to predict which, if any, other Factor V mutations are associated with thrombosis.

We determine that the Examiner did not err in rejecting claims 46, 53, 64, and 65 as lacking a sufficient enabling disclosure under 35 U.S.C. § 112, ¶1.

Claims 54 and 55

Appellants argued claims 54 and 55 together. We select claim 54 as representative. Bd. R. 37 (c)(1)(vii).

Claim 54 recites:

> A method for determining a presence of a Factor V gene mutation associated with Activated Protein C (APC)-resistance in an individual at risk for APC-resistance, the method comprising the steps of
>
> (a) obtaining a sample from the individual;
>
> (b) conducting a nucleic acid sequencing assay on the sample using reagents specific for the Factor V gene to determine the Factor V gene sequence; and
>
> (c) determining the presence of the Factor V gene mutation associated with APC resistance in the individual by comparing the sequence of the Factor V gene from step (b) to a normal Factor V gene sequence.

Claim 54 is directed to a method of "determining the presence of a Factor V gene mutation associated with APC-resistance in an individual at risk for APC-resistance." The recited method requires nucleic acid sequencing, to determine if a mutation associated with APC resistance is present in an individual who is "at risk for APC-resistance." Claim 54 does not recite any specific mutation of the Factor V gene (FF 9), and so encompasses detecting all mutations of the Factor V gene that are associated with APC resistance. We conclude that claim 54 is not enabled for many of the same reasons discussed above regarding claim 46. The state of the art was unpredictable at the time of filing, as evidenced by the references cited by the Examiner. Without disclosure of Factor V mutations sufficient to support the genus of Factor V mutations that are associated with risk of APC-resistance, those in the art would have had to conduct undue experimentation to carry out the full scope of the claimed method.

Appellant presented some of the same arguments against the rejection of claims 54 and 55, as for the rejection of claims 46, 53, 64, and 65, explained above. Appellant argued that "knowledge of a specific mutation in the Factor V gene is not required to practice the invention as claimed in claim 54" (App. Br. at 11), because the association between Factor V and APC-resistance is based on "clinical and biochemical evidence." (*Id.*). Appellant asserted further that "[s]ince claim 54 requires obtaining a sample from an individual known to have or to be at risk for APC-resistance, the mutation determined in the individual's Factor V gene by conducting a nucleic acid sequencing assay on the same as recited in claim 54 would naturally be associated with APC-resistance." (App. Br. at 11-12).

Appellant cited references that teach the Factor V cDNA and genomic DNA sequences. (*Id.*). Appellant also argued that references such as Shen demonstrate the high degree of skill and knowledge of sequencing technology, which would have allowed those in the art to perform the necessary methods and to determine which mutations were silent or conservative. (*Id.* at 12-13).

At the outset, we note that Appellant asserted claim 54 "requires obtaining a sample from an individual *known to have* or to be at risk for APC-resistance." *See* App. Br. at 12 and Reply Br. at 10. But, the language of claim 54, as provided in the Claims Appendix to Appellant's Appeal Brief, recites only "an individual at risk for APC-resistance,"[2] and does not include individuals who are known to have APC-resistance. This language is not clearly defined in Appellant's Specification (FF 10)[3], but we understand "individuals at risk" to mean these people who are more likely *to develop* APC-resistance than a normal individual. (FF 11). Appellant's have directed us to no basis for expanding the scope of the ordinary meaning of "individuals at risk" to include those who already are known to have APC resistance.[4]

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[2] We review the claims as recited in the Claims Appeal. *See* Bd. R. 41.37(c)(1)(viii).

[3] It would seem to us that one either suffers from APC resistance or does not. However, taking claim 54 as Appellant choose to draft it, we determine that Appellants have not provided evidence showing that one skilled in the art would have been able to determine what Factor V mutations are associated with "an increased risk of APC resistance".

[4] In fact, we found the argument in the Reply Brief to be somewhat misleading. In particular Appellant underlined the claim phrase "in an individual at risk for APC-resistance" while asserting that "[c]laim 54 requires obtaining a sample from an individual known to have APC-resistance or be at risk for APC-resistance . . . ." (Reply Br. at 10). No

Appellant's specification does not teach how to determine who is more likely to develop APC-resistance. (FF 12). Thus, even if those in the art would have known the Factor V gene and genomic sequences and would have had the skills to perform sequencing and perform and determine which mutations were silent or conservative, they would not have known on which individuals to carry out these procedures. Nor has Appellant provided evidence showing that any mutation in the Factor V gene would have been associated with APC resistance. Furthermore, Appellant's argument that "the mutation determined in the individual's Factor V gene . . . would naturally be associated with APC-resistance" (App. Br. at 12) seems to apply only to individuals known to have APC-resistance and is unpersuasive as unsupported attorney argument at any rate.

Appellant's Specification has not set out even a single mutation having an association with a *risk* of APC-resistance. The evidence before us indicates that the determination of Factor V mutations associated with a risk of APC resistance is subject to the same unpredictability described above as to claim 46 for determining which individuals are at risk for developing thrombosis. Specifically, the references cited by the Examiner, Pennisi, Blumenfeld, Bertina, de Visser, and Price, show the unpredictability in the field of genetic prediction of disease risk in general, and of genetic prediction of APC-resistance, specifically.

Appellant points to Voorberg to show the success of Appellant's claimed method using techniques known in the art. (*Id.* at 14). Appellant asserts that Voorberg "showed that the patients having APC-resistance contained an abnormal sequence at position 506, a Gln instead of a normal

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explanation was given for this inconsistency.

Arg." (*Id.*). The claimed method, though, is not drawn to determining the presence of a Factor V gene mutation in an individual who has APC-resistance, but, instead, in "an individual at risk for APC-resistance." (FF 8). Because Appellant has not provided any gene structures that are predictive of APC-resistance, and studies to find such structures are subject to the same unpredictability discussed above, Voorberg does not contribute to enablement of claim 54.

We determine that the Examiner did not err in rejection claims 54 and 55 under 35 U.S.C. § 112, ¶1, for failure to provide an enabling disclosure.

VI. ORDER

Upon consideration of the record and for the reasons given, the Examiner's rejection of claims 46, 53-55, 64, and 65 under 35 U.S.C. § 112, ¶ 1, as lacking enablement is AFFIRMED.

AFFIRMED

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